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TESTS OF SECOBARBITAL

Secobarbital capsules purchased from 36 drug companies were tested for conformance to U.S. Pharmacopeia specifications, in the second of The Medical Letter's series of assays of prescription drugs. All samples passed the identification test for secobarbital, and each met the requirement that the combined contents of 20 capsules fall between 90% and 105% of the declared weight. Samples obtained from Eli Lilly, the principal brand-name supplier of secobarbital (Seconal), and from 26 other companies, conformed fully to USP requirements. Samples from nine companies showed excessive weight variation from capsule to capsule; one sample showed a capsule-to-capsule variation of from -41% to +40%.

SELECTION OF COMPANIES - In the tests of prednisone tablets (The Medical Letter, 2:65, Aug. 19, 1960), samples were obtained from the major drug companies and from a random selection of smaller companies. For the secobarbital tests, however, most of the samples were purchased from companies which supply a large variety of prescription drugs. This change in practice was made in recognition of the fact that no single drug assay provides a reliable guide to the quality of a company's products, and with the hope that in repeated tests of different products from the same companies, a pattern would emerge to indicate which companies maintain adequate quality controls.

Most of the samples tested were purchased before October 1, 1960, the date on which the Sixteenth Revision of the U. S. Pharmacopeia superseded the Fifteenth Revision. Since the standards for weight variation of capsules differ in the two editions, the test results were evaluated in terms of both standards. Where a sample fell below the stricter USP XVI standards, a new sample was later purchased from the same company and subjected to the weight variation test. Of the new samples tested in this way, five failed to meet the requirements of USP XVI and were substandard.

WEIGHT VARIATION - The USP limits the weight variation from capsule to capsule to a certain percentage of the average weight of the capsules in a sample. The Fifteenth Revision of USP permitted one-tenth of the capsules in a sample to vary from the average weight by more than 15%, provided no capsule in the sample differed from the average weight by more than 30%. The stricter Sixteenth Revision permits one-tenth of the capsules in a sample to vary from the average by more than 10%, provided no capsule differs by more than 25%. In accordance

RESULTS OF TESTS OF 100-MG. SECOBARBITAL CAPSULES

Samples purchased from the following companies met USP requirements (figures show average weight of 20 capsules as a percentage of labeled weight, and price for 1000 capsules):

Allen Pharm.	101%	$ 8.00	Eli Lilly	103%	$18.30
Amer. Drug. Prod.	97	5.50	Massengill	100	16.00
Amer. Pharm. (APC)	92	11.40	Panray	104	7.20
Approved Pharm.	105	9.00	Penhurst Pharm.	101	8.50
Brewer	98	8.50	Premo Pharm. Labs.	103	11.80
Bryant Pharm.	101	7.20	Robinson Lab.	101	7.75
Columbia Medical	100	5.95	Stanley Drug Prod.	96	7.75
Darby Drug (Bio-Intrasol name on label)	98	5.00	Supreme Pharm.	99	9.60
			Testagar	95	10.80
Gotham Pharm.	102	6.54	Vitamin Research	103	7.21
Hance Bros. & White	99	6.70	Vitamix	102	8.00
Harvey Labs.	99	10.75	Vitarine	105	10.80
Kirkman Pharm.	101	7.50	West-ward	105	9.30
Lannett	100	9.00	Wolins Pharm.	99	5.25

One or both of the samples purchased from each of the following companies exceeded USP limits for weight variation. The first sample was considered substandard if it failed to meet the requirements of USP XV; the second, purchased at a later date, if it failed to meet the more stringent requirements of USP XVI:

Company		Per cent of Labeled Weight	Weight Variation from Average	Capsules Weighed	Price-1000 Capsules
Cowley Pharm.	1st sample	99	9 caps. above 10% but meets USP XV.	60	$ 6.50
	**2nd sample	—	10% to 25%, 12 caps.	60	
Robert Daniels	*1st sample	105	15% to 30%, 9 caps.; more than 30%, 3 caps.	60	7.20
	2nd sample	—	all less than 10%	20	
DuMont Pharm.	1st sample	104	2 caps. above 25% but meets USP XV.	60	5.95
	**2nd sample	—	more than 30%, 2 caps.	20	
Haack Labs.	1st sample	100	9 caps. above 10% but meets USP XV.	60	8.00
	**2nd sample	—	10% to 25%, 5 caps.; more than 25%, 2 caps.	20	
Jan Labs.	*1st sample	93	15% to 30%, 6 caps.; more than 30%, 8 caps.	60	5.85
	2nd sample	—	all less than 10%	20	
Moore Chem.	*1st sample	96	15% to 30%, 3 caps.; more than 30%, 1 cap.	60	4.75
	2nd sample	—	all less than 10%	20	
Nysco Labs.	1st sample	100	16 caps. above 10% but meets USP XV.	60	4.50
	**2nd sample	—	10% to 25%, 9 caps.	60	
Raway Pharm.	*1st sample	93	15% to 30%, 8 caps.	60	6.25
	**2nd sample	—	10% to 25%, 11 caps.; more than 25%, 1 cap.	60	
Wales Chem.	*1st sample	100	15% to 30%, 2 caps.; more than 30%, 2 caps.	20	5.75
	2nd sample	—	all less than 10%	20	

*substandard, USP XV. **substandard, USP XVI.

with the provisions of the standard, 20 capsules taken from each sample were weighed individually, with an additional 40 capsules weighed if from three to six of the first 20 capsules varied from the average weight by more than the lower USP limits (15% or 10%) with none above the upper limits (30% or 25%).

A total of 1500 capsules were weighed individually in the tests, with the following results:

1324 (88%) varied by less than 10% from the average weight.
146 (10%) varied by more than 10% but less than 25% from the average weight.
30 (2%) varied by more than 25% from the average weight.

CLINICAL SIGNIFICANCE - The test results for each sample are shown in the table. None of the samples tested could be considered to offer a hazard to the patient taking them; nevertheless, a significant number were substandard, and an occasional capsule in these samples would provide either inadequate or excessive dosage – a factor to be considered by the physician in deciding whether to prescribe by brand name or to permit the patient to make some saving by prescribing generically. The list prices (to the pharmacist) of the capsules purchased for the tests ranged from $4.50 to $18.30 per thousand. When 100-mg. capsules are prescribed in quantities of 30, the cost to the patient is about 4¢ to 7¢ per capsule.

The secobarbital capsules (all 100-mg. or 1 1/2 gr.) were purchased from the various companies by pharmacists in no way associated with The Medical Letter. The samples – identified only by a code number – were tested for The Medical Letter by a qualified independent commercial laboratory.

RETICULOSE

Reticulose (Chemico Labs.) is being promoted to physicians as a broad-spectrum antiviral drug. The manufacturer describes it as a lipoprotein-nucleic acid complex able "to rapidly inhibit the course of a variety of viral diseases, particularly in the acute stage." The manufacturer's brochure states that over 500,000 injections have been given with no reported toxic manifestations, and that "hundreds of cases show Reticulose to be a definite anti-viral biotic."

There is no credible evidence that this drug has any value whatsoever. The kind of evidence offered for Reticulose – uncontrolled observations of the effects of a drug in infections with marked variation in duration and severity – can be disregarded.

THE EVIDENCE - The only animal study supporting the claims for Reticulose is in the form of composite curves which indicate a protective effect of the drug against the hematologic damage produced in rabbits by irradiation (R. M. Thompson, Military Surgeon, 110:51, 1952). There are no reports of trials of the drug in animals infected by any virus. As for clinical evidence, enthusiastic but uncontrolled testimonial case reports are offered in several journals and in a recent symposium sponsored by the manufacturer. Results bordering on the

miraculous are reported in generalized vaccinia, herpes gestationis, herpes zoster, herpes simplex, colds, influenza, infectious mononucleosis, viral encephalitis, and hepatitis. The reports cited in the manufacturer's literature include many by recognized authorities on viral diseases, but the references are to statements by these authorities on the nature of viruses or viral disease; none of them had a word to say about Reticulose or the theoretical or practical usefulness of a lipoprotein-nucleic acid complex.

TIGAN

Trimethobenzamide (Tigan - Roche) is offered as a broad-spectrum antiemetic for the nausea and vomiting of pregnancy, travel sickness, gastrointestinal conditions, operative procedures, carcinomatosis, and other disorders. Animal experimentation indicates that Tigan, like other antiemetic drugs, acts through the "chemoreceptor trigger zone" (CTZ) in the brain stem. At best, therefore, effective antiemetic action could be expected only where the stimulus is relayed through the CTZ, as after the use of digitalis or morphine; significant effects cannot be expected where the stimulus goes directly to the vomiting center, as with gastric or peritoneal irritation, and probably in psychogenic vomiting.

CLINICAL TRIALS - The clinical evidence supporting the claims for the drug is not impressive despite the fact that a high degree of effectiveness is claimed in vomiting from a great variety of causes. With few exceptions, controls were absent or inadequate in the trials. A. L. Kolodny, Am. J. Med. Sci., 239:682, 1960) reported that Tigan was effective in most of the 95 patients who received it; the study was remarkable in that not one of 66 patients on placebo became completely free of nausea and vomiting – a result that is difficult to understand in a disorder which is usually self-limited.

In the only controlled trial in which Tigan was matched against both a phenothiazine and a placebo in the prevention of postoperative nausea and vomiting (J. W. Bellville, et al., Clin. Pharm. and Ther., 1:590, 1960), the incidence of nausea and vomiting was 14.2 per cent with placebo; 14 per cent without treatment; 12.3 and 12 per cent, respectively, after 100 mg. and 200 mg. of Tigan administered intramuscularly; and 6.5 and 6.6 per cent, respectively, after 2.5 and 5 mg. of perphenazine (Trilafon) intramuscularly. If Tigan had any effect, it was much less than that of Trilafon. It has thus not been shown that Tigan is more effective or even as effective as other antiemetic drugs.

When nausea and vomiting cannot be prevented or relieved by removal of the causes, symptomatic relief can often be obtained by administration of barbiturates; of antihistamine drugs, such as diphenhydramine (Benadryl - Parke, Davis), dimenhydrinate (Dramamine - Searle), meclizine (Bonine - Pfizer), and cyclizine (Marenzine - Burroughs Wellcome); of phenothiazines, such as chlorpromazine (Thorazine - SKF), prochlorperazine (Compazine - SKF), perphenazine (Trilafon - Schering), triflupromazine (Vesprin - Squibb); or of promethazine (Phenergan - Wyeth), which is both an antihistamine and a phenothiazine. In view of the occasional serious side effects of phenothiazines, a barbiturate or an antihistamine should probably be tried first.

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